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Health and Environmental Effects Profile for Molinate

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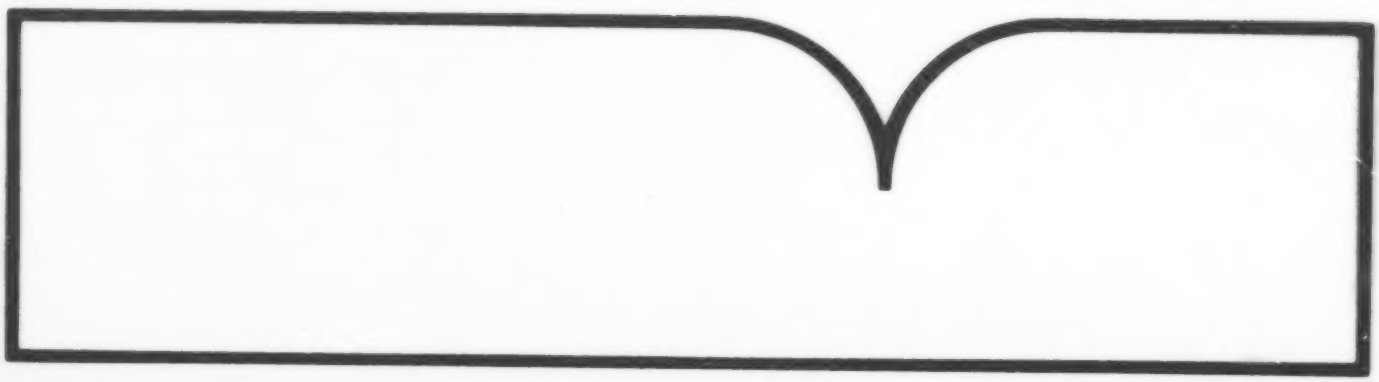

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR MOLINATE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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16. ABSTRACT

The Health and Environmental Effects Profile for molinate was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Molinate has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for molinate is 6.3×10^{-4} (mg/kg bw/day) for oral exposure.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

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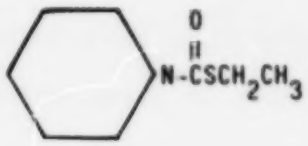
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCI	Bioconcentration factor
DNA	Deoxyribonucleic acid
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
ppb	Parts per billion
ppm	Parts per million
RNA	Ribonucleic acid
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Molinate is the common name for 1-H-azepine-1-carbothioic acid, hexahydro-, S-ethyl ester. It is also known as ethyl 1-hexamethyleneiminecarbothiolate (SRI, 1983) and S-ethyl hexahydro-1H-azepine 1-carbothioate (Plimmer, 1978). This compound was introduced into the market in 1954 under the code number R-4572 and has the trade names, Ordam and Hydram. The structure of molinate is depicted below:



Molecular formula: $C_9H_{17}NOs$

Molecular weight: 187.3

The Chemical Abstract Service (CAS) Registry number for this compound is: 2212-67-1.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Molinate is a clear, light yellow liquid with an aromatic odor (BCPC, 1977). Some of the physical properties are listed below:

Boiling Point:	137°C at 10 mmHg (Ouellette and King, 1977)
Vapor Pressure at 25°C:	5.6×10^{-3} mmHg (Ouellette and King, 1977; BCPC, 1977)
Solubility in water:	800 mg/ℓ at 21°C (Ouellette and King, 1977; BCPC, 1977; Kenaga, 1980)
Density:	1.065 g/cm³ at 20°C (BCPC, 1977)
Evaporation rate at 20°C:	50% in 1 day (Strekozov et al., 1979)

Molinate is also soluble in acetone, benzene, 2-propanol, methanol and xylene. It is stable to hydrolysis and is noncorrosive (BCPC, 1977).

1.3. PRODUCTION DATA

Molinate is prepared by the reaction of S-ethyl chlorothioformate and hexamethyleneimine (BCPC, 1977). It is produced by the Stauffer Chemical Company at Cold Creek, Alabama (SRI, 1983; Ouellette and King, 1977). Data regarding production of this compound in the United States were not available.

1.4. USE DATA

Molinate is used as an herbicide to control watergrass in rice fields. It is applied either before planting to water-seeded or shallow soil-seeded rice, or postflood, postemergence on other types of rice culture (BCPC, 1977).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

The fate and transport of molinate in water and soil have been studied extensively because it is the principal herbicide used in rice production. The fate of molinate in aqueous medium is likely to be determined by its ability to undergo biological and chemical reactions. Photochemical reactions, free radical reactions and hydrolytic reactions are three likely classes of chemical reactions that may influence the fate of molinate in water. Draper (1979) found that molinate was unstable to sunlight or simulated sunlight in the presence of traces of hydrogen peroxide (μM levels). Photooxidation of the chemical occurred in natural water but not in distilled water. Other experiments indicated that natural sensitizers and trace oxidants in solution are important for the photodecomposition of a few herbicides including molinate. Brooks (1980) reported that molinate did not decompose in aqueous solution in simulated sunlight, but had a half-life of 10 days when traces of tryptophan (present under field conditions in California) were detected. Similar results obtained by Crosby (1979) indicated that molinate was stable to UV light from sun in distilled water, but under field conditions molinate reacted in the presence of sunlight and tryptophan to provide its S-oxide and 2-oxo analog, which subsequently were converted to other products.

Available data suggest that microbial degradation contributes significantly to the disappearance of molinate from the aqueous environment. In a Russian study, Golovleva et al. (1981) reported that the main products of microbial degradation of molinate in ponds were β-hydroxyordam, γ-hydroxyordam and ketoordam. These compounds were detected within 7 days following herbicide application. Degradation appeared to be accomplished by 46 strains of bacteria, with Norcardia being the most prominent. In an earlier

study, Golovlev et al. (1980) concluded that under actual conditions in rice fields where concentrations of molinate did not exceed several mg/ℓ of water, rhodococci (coryneform bacteria), bacilli and some cocci were capable of extensive transformation of the parent compound. In a Russian abstract, Klysheva et al. (1980) identified Bacillus as the main group of microorganisms that cometabolized 5.0 mg/ℓ molinate in the presence of sucrose within 5-7 days. Sucrose also enhanced the degradation of molinate by Norcardia and Streptomyces. The rate of molinate degradation in this study depended on aeration conditions; in anaerobic environments, the rate was greatly reduced. Results of experiments under simulated flooded conditions determined that molinate was degraded biologically through oxidative metabolism of microorganisms, since no significant degradation was detected in sterilized controls or anaerobic environments (Deuel et al., 1978).

Dissipation of molinate in water appears to occur quite readily under anaerobic conditions. Half-lives were reported as <100 hours in flooded rice fields (Deuel, 1975); 3 days in rice paddy water (Podlejski and Dervieux, 1978); and 4 days in rice paddies and river water (Anonymous, 1979). Field experiments conducted under flooded rice cultivation determined the persistence and half-life of molinate with respect to intermittent and continuous flow irrigation schemes. At application rates of 3.4 and 11.2 kg/ha of molinate, persistence at statistically significant ($p=0.05$) levels ranged from 96-384 hours, and half-life values averaged 96 ± 22 hours in intermittent flow plots and 54 ± 17 hours in continuous flow plots (Deuel et al., 1978). Molinate persisted in seepage waters of submerged soils for ≥ 4 months, possibly because anaerobic conditions (Tanji et al., 1974).

Volatilization of molinate from distilled water and simulated rice paddies was measured by Deuel et al. (1978). Results of laboratory experiments indicated that at 30°C a maximum of 6 g of molinate would volatilize from a 300 m^2 surface of distilled water in 1 day and 2.4 g/day would be vaporized from water with a colloidal load of 100 mg/ℓ. These values were well below the average 30 g/day dissipation from field plots; thus, volatilization was not a primary mode of dissipation under the conditions of this study, but the cumulative loss over a period of time may be significant under hot, windy conditions (Deuel et al., 1978). In a Russian study, Popovich (1982) measured 2.2, 2.0 and 0.35 mg/m^3 of molinate in the air over rice paddies 6, 7 and 8 days, respectively, after irrigation; however, no original concentration was reported.

Few data were found that described the aquatic transport of molinate. In a Russian study, Golovleva et al. (1981) found that following the addition of 6.2-16.5 mg/ℓ molinate to ponds, sorption by mud occurred at $\leq$4.3 mg/100 g of solids. These data suggest that sorption onto particulate matter may contribute significantly to the transport of this compound in aquatic media.

A BCF of 26 measured experimentally by Kanazawa (1982), and a BCF value of 14 predicted from binary regression equations (Kenaga, 1980) suggested that bioaccumulation of molinate in aquatic organisms is unlikely.

Molinate is an herbicide used to control weeds in rice paddies; therefore, almost all available studies have discussed the fate of this compound under flooded soil conditions. Photodecomposition of molinate from flooded soil surfaces is likely to be similar to the processes previously described for water. Strekozov et al. (1979) noted that the complete photolysis of molinate on glass surfaces required 1 day under laboratory conditions. This

information can be relevant to soil surfaces. Natural sensitizers, such as tryptophan, that appear to be necessary for the photodecomposition of molinate (Brooks, 1980; Crosby, 1979) have been found in rice fields. Thus, it is likely that photodegradation of this compound can occur on soil surfaces.

Microbial degradation is likely to be a major factor in the disappearance of molinate in the soil. The microorganisms capable of metabolizing molinate in water (e.g., Norcardia, Bacillus) are also indigenous to soil (Atlas and Bartha, 1981). In a Russian study, Strekozov et al. (1979) reported that 4 days after application of 5 kg/ha of molinate to barley fields, ~20% was lost to biological transformation. Loss of molinate from soils by microbial degradation may be influenced by the nature of the soil. For example, in soils with a moderate adsorptive capacity, herbicides are subjected to significant degradation by microorganisms (Koren et al., 1968). In soils with a high adsorptive capacity, degradation by microorganisms may be retarded. In a Russian study, Vernichenko and Kovtun (1977) found that 1 day after application of 7.4 kg/ha of molinate, the top 10 cm of soil contained 3400 µg/kg. Within 1 month the content of molinate decreased to 118 µg/kg and within 3 months, to 55 µg/kg. The authors noted that initial decomposition was retarded by adsorption of the compound to soil particles, and that the rate of decomposition was slower in the 20-40 cm soil layer. Tanji et al. (1974) attributed the prolonged persistence ($\geq$4 months) of molinate in flooded soils to the binding of residues to soil constituents, thus rendering the compound unavailable for microbial degradation.

Anaerobic conditions have been found to retard microbial degradation of molinate in aqueous media (Klysheva et al., 1980; Tanji et al., 1974; Deuel et al., 1978; Golovleva et al., 1981). Although no data are available, anaerobic conditions in the soil may have the same effect on microorganisms.

The transport of molinate in the soil is likely to occur through volatilization or leaching. In a Russian study, Strekozov et al. (1979) estimated that 50% of an initial application of 5 kg/ha molinate to barley fields was volatilized within 1 day. It is likely that volatilization may contribute to the transport of this compound into the atmosphere. The leaching of molinate from soil is directly related to its water solubility and inversely related to the organic content of the soil (Koren et al., 1969). Gray and Weirich (1968) measured the rate of leaching of molinate in five soil types with clay contents ranging from 5-17.6% and organic matter contents ranging from 0.8-34.6%. The depth of leaching decreased as the clay content and organic matter of the soil increased. Molinate was found to leach very rapidly in all five soils. Strekozov et al. (1979) found molinate to have a high mobility in soils with most of the herbicide disappearing within 4 days following application of 5 kg/ha.

Limited information was located concerning the fate and transport of molinate in the atmosphere. It is likely that volatilization from soil or water surfaces would be a significant mode of entry of this compound into the atmosphere. The fate of molinate in the atmosphere will depend on its reactions with O_3, NO_x and free radicals (RO•, O• and RO_2•) and its ability to undergo photolysis. Molinate in the vapor phase can react with UV light in the air to form a substituted 2-piperidone and a piperidine (Brooks, 1980).

Information of the transport and fate of molinate in the atmosphere was not available from the sources searched for this study (see Appendix). Based on the soil sorption coefficient of 110 predicted from binary regression equations (Kenaga, 1980) and the relatively high solubility of this compound (800 mg/ℓ), it is possible that the removal of particulate sorbed molinate will occur through both dry and wet deposition.

3. EXPOSURE

No monitoring information on molinate was located in STORET. One Japanese study reported that molinate was found in concentrations of 62.9 ppb in creek water during July and August of 1978 (Mikuriya and Miyahara, 1979). Korzhevenko et al. (1977) sprayed 5 kg/ha of molinate over a closed pond in Russia and found an unspecified amount of residue in fish 30 days after application.

4. PHARMACOKINETICS

4.1. ABSORPTION

Specific data on the absorption of molinate were unavailable; however, some information was obtained from metabolism studies. DeBaun et al. (1978a, 1979) recovered ~88% of the radioactivity of [ring-^{14}C]-molinate (S-ethylhexahydro[2-^{14}C]azepine-1-carbothioate) within 48 hours in the urine of rats dosed with 72 mg/kg by gavage. In a Russian study, Stepanchenko (1974) orally administered 300 mg/kg to rats and found accumulation in tissues and monitored distribution in the blood at 30 minutes to 4 days after dosing. These studies indicated that molinate is rapidly absorbed through the gastrointestinal tract.

4.2. DISTRIBUTION

DeBaun et al. (1978b) investigated the distribution of ^{14}C radiolabel in tissues and organs of six female and six male Simonsen albino rats dosed by gavage with 72 mg/kg [ring-^{14}C]-molinate (S-ethyl hexahydro[2-^{14}C]-azepine-1-carbothioate). One day after dosing, the highest concentration of radioactivity was found in the blood, followed by the liver, kidneys, lungs, spleen and heart. Residues in most tissues decreased over the 7-day period after dosing. Expressed as a percent administered ^{14}C, the whole body residues accounted for an average of 13.8% (day 1), 5.2% (day 3) and 3.7% (day 7). An exception to this was the persistently high level in the blood, which may also have contributed to the high 7-day values of other "blood rich" tissues such as the liver, kidney, heart, lungs and spleen. To determine the relationship between dose and residual ^{14}C in the blood, three male rats were administered radiolabeled molinate ([ring-^{14}C]) orally at doses of 5, 20 or 80 mg/kg. The ppm molinate equivalent in the blood 7 days after dosing was ~4.5 times greater after the 80 mg/kg dose compared with

the 20 mg/kg dose, and was ~9.9 times greater after the 20 mg/kg dose compared with the 5 mg/kg dose, suggesting that residue accumulation of ^{14}C was dose-dependent. The authors noted that precipitation of erythrocytes by centrifugation showed that virtually all the blood ^{14}C residues were associated with the precipitated cellular fraction.

Abstracts of two Russian studies described the distribution of orally administered molinate in rats. Aleksandrova and Klisenko (1978) reported that an unspecified dose of molinate was rapidly detoxified and the metabolites were detected in the tissues for 0.5-24 hours and in the blood for 2 days. When administered orally to rats at a dose of 300 mg/kg, molinate accumulated in the brain and to a lesser extent in the liver, kidney, lung, heart and spleen (Stepanchenko, 1974).

4.3. METABOLISM

Metabolism of molinate has been studied in mice and rats in both *in vivo* and *in vitro* systems.

DeBaun et al. (1978a, 1979) administered 72 mg/kg [ring-^{14}C]-molinate by gavage to male and female Simonsen albino rats. Molinate was metabolized extensively within 48 hours to five polar metabolites that accounted for ~87% of the urinary ^{14}C. Unchanged molinate accounted for only 0.1% of the urinary ^{14}C. The two major metabolic pathways were identified as involving sulfoxidation and conjugation with glutathione to ultimately give rise to a mercapturic acid derivative accounting for 35.4% of the urinary ^{14}C and ring hydroxylation to give 3- and 4-hydroxy molinate derivatives (0.8% free and 26.1% as O-glucuronides). Two basic metabolites formed by the hydrolysis of sulfoxidized molinate and its hydroxy derivatives were hexamethyleneimine and 3- and 4-hydroxyhexamethyleneimine, accounting for 14.6 and 10.3%, respectively, of the radioactivity in the urine.

Casida et al. (1974, 1975) studied the sulfoxidation of molinate by mice in vivo and by mouse liver microsomes in vitro. Preparations of molinate in 50 µl dimethylsulfoxide were administered by intraperitoneal injection at 1 or 2 mmole/kg. The sulfoxide of molinate was detected in the liver 10 minutes after treatment, but was barely detectable 60 minutes after administration. The sulfone of molinate was not detected in the liver, but it was not expected to persist because it is hydrolytically unstable (Casida et al., 1975).

When molinate was incubated with mouse liver microsomes and NADPH, molinate sulfoxide was detected as the major metabolite. A volatile "mercaptan" was liberated when the soluble enzymes and glutathione (GSH) were added to the incubation system. These results suggested that the reaction of molinate sulfoxide with GSH resulted in a cleavage of the carbamoyl bond. It appeared that GSH S-transferase (or transferases) catalyzed the attack of GSH at the carbonyl group (Casida et al., 1974).

4.4. EXCRETION

DeBaun et al. (1979) reported that excretion of ^{14}C from Simonsen albino rats that had been given an oral dose of 72 mg/kg of [ring-^{14}C]-molinate was 95% complete within 48 hours. The major routes of excretion were via the urine and feces. Less than 0.1% of the administered dose was excreted in the respired air within 48 hours. In an earlier study, DeBaun et al. (1978a) found 97% excretion within 48 hours after an oral dose of 72 mg/kg [ring-^{14}C]molinate to rats. The majority of ^{14}C excreted was present in the urine (88%) and feces (11%), with <1% excreted in expired air.

5. EFFECTS

5.1. CARCINOGENICITY

No information was found on the carcinogenicity of molinate; this compound is not scheduled for testing by the National Toxicology Program (NTP, 1983).

5.2. MUTAGENICITY

Molinate was not shown to induce reverse mutations in the spot test with any of eight strains of histidine-dependent mutants of Salmonella typhimurium; the S-9 metabolic activating fraction was not employed (Anderson et al., 1972). Shirasu et al. (1976) also reported that molinate failed to induce reverse mutations in the absence of S-9 in spot tests with auxotrophic strains of Escherichia coli (WP2) and four strains of histidine-dependent Salmonella typhimurium (TA1535, TA1536, TA1537 and TA1538). Molinate was not mutagenic to any of the five strains of Salmonella typhimurium (TA1535, TA1537, TA1538, TA98 and TA100), whether in the presence or absence of S-9, when 10-1500 µg/plate was incorporated into the medium (De Lorenzo et al., 1978). Negative results were obtained in the rec-assay with repair deficient and proficient strains of Bacillus subtilis in the absence of a metabolic activating system (Shirasu et al., 1976).

Molinate has been classified as a mutagen (NIOSH, 1983) based on a Russian study by Kurinnyi (1977), who found that molinate concentrations of 0.02 and 0.2 µg/ml increased the frequency of chromosomal aberrations in human lymphocytes in culture. In a Russian study, increased frequency of chromosome aberrations in bone marrow cells was reported after administration of high (unspecified) doses of molinate to mice (Kuz'menko et al., 1980).

5.3. TERATOGENICITY

One Russian study available in abstract form described the immunological reactivity of the progency of rats affected by molinate. Olefir (1978a) reported that repeated exposures of pregnant rats to an unspecified dose (1% of LD_{50}) of molinate in air decreased the activity of nonspecific factors of immunity, the protective properties of the skin and mucus, and the resistance to infection in the first-generation offspring.

5.4. OTHER REPRODUCTIVE EFFECTS

Two Russian studies available only in abstract form described the effect of molinate on the reproductive processes in rats. Anina et al. (1975) observed decreased motility of spermatozoids in males and decreased fertility in females following the oral administration of molinate at a dose of 3.6 mg/kg/day to rats for 2 months. The herbicide also decreased the levels of RNA and DNA and increased the activities of RNase and DNase in the testicles. Similarly, Voitenko and Medved (1973) found that young rats given 3.6 mg/kg/day of molinate orally for 2 months showed impaired spermatozoid function and gonadal nucleic acid metabolism and oxidative processes. Treated females mated with untreated males exhibited increased resorption of fetuses and increased postnatal death of their offspring, as well as abnormalities in development.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Several Russian studies available in abstract form described the effects of subchronic exposure of rats to molinate.

Over 9 months, doses of 6.5 mg/kg (unspecified route of administration) produced changes in adrenal function, reductions in body temperature, disturbances in oxidation enzyme activities and reduction in hemoglobin concentration in an unspecified animal (Vrochinskii et al., 1975). These effects

were not observed at doses of 0.65 mg/kg. Olefir (1973) administered to rats an unspecified dose (1/20 of LD_{50}) of molinate 5 times/week for 4.5 months and found significant inhibition of the nonspecific immunobiological reactivity of the animals for up to 2 months after the dose was discontinued. A decrease in the resistance of the treated rats to a staphylococcal infection was also observed. Disorders in the immune system were also reported in rats after 3.5 and 4 months of repeated treatment with an unspecified dose corresponding to 1/20 of the LD_{50} (Olefir, 1971; 1978b). Bakhtizina and Latypova (1976) observed morphological and functional changes in the anterior pituitary, thyroid and gonads of rats after chronic treatment with molinate; however, dose and length of treatment were not specified.

5.6. OTHER RELEVANT DATA

Oral LD_{50}s ranged from 50 mg/kg in the rat to 795 mg/kg in the mouse (NIOSH, 1983). In a Russian study, an intraperitoneal LD_{50} in mice of 530 mg/kg was identified (Dyadicheva, 1969); and LD_{50}s of 720 mg/kg in the rat and 720 mg/kg in an unknown mammal were reported for unspecified routes of administration (NIOSH, 1983).

Abstracts of Russian studies have provided limited information on the acute toxicity of molinate. In acute experiments with rats, 300 mg/kg decreased serum lysozyme, phagocytic activity, the absorptive capacity of the reticulo-endothelial system and the skin phagocytic index (Olefir and Karpenko, 1971). The observed effects in rats of oral acute poisoning by a single dose of molinate (1/20 of LD_{50}) included hypotonia, bradycardia and a decrease in respiration frequency (Matokhnyuk, 1972). Oral doses corresponding to 0.01 of the LD_{50} given to sexually immature male rats decreased the levels of DNA and RNA in the gonads (Anina, 1975), and exposure of rats to molinate at an unspecified dose from birth delayed general growth

and sexual development (Bakhtizina, 1976). Inhalation of molinate at an unspecified concentration was "moderately toxic" to cats and rats, particularly affecting the nervous system and endocrine glands (Dyadicheva, 1970). Molinate did not produce any reaction in guinea pigs when 0.25 or 2.5% solutions were applied dermally (Latypova and Murzakaev, 1976).

6. AQUATIC TOXICITY

6.1. ACUTE

Acute toxicity tests of molinate have been conducted with at least 11 species of freshwater invertebrates, 8 species of freshwater fish and amphibians and several marine species (Table 6-1). As shown in Table 6-1, acute LC_{50} values ranged between 0.18 and 15.9 mg/ℓ for arthropods, 0.21 and 34.5 mg/ℓ for fish, and 14 and 34 mg/ℓ for amphibians, indicating a similar range in sensitivity among species in each of these groups. In contrast, the 96-hour LC_{50} value for a clam species, Rangia cuneata, was 197 mg/ℓ, suggesting that molluscs may be less sensitive to molinate. Butler (1965) reported that a marine mollusc species was less sensitive than marine fish and shrimp species. The shell growth of oysters, Crassostrea virginica, was not affected during the 96-hour exposure to molinate, whereas 48 hours of exposure to the same molinate concentration caused 20% mortality in spot, Leiostomus xanthurus, and 30% mortality in shrimp, Penaeus aztecus.

6.2. CHRONIC

Subchronic toxicity tests have been conducted with at least two freshwater fish species. Kawatsu (1977) reported that the 21-day LC_{50} value of molinate to carp, Cyprinus carpio, was 0.18 mg/ℓ. Perevozchenko (1975) reported that exposure to 1.4 mg/ℓ for 45 days caused 50-60% mortality and inhibition of brain acetyl-cholinesterase activity in loach, Misgurnus fossilis. Pertinent data regarding the effects of exposure to molinate through longer periods were not located in the available literature.

6.3. PLANT EFFECTS

Pokrovskaya and Matsudov (1976) reported that molinate at concentrations as low as 10^{-4} M (18.7 mg/ℓ) inhibited the growth of algae, Nostoc

TABLE 6-1

Acute Toxicity of Molinate to Aquatic Animals

Species	LC_{50} (mg/ℓ) 24-hour	48-hour	96-hour	Reference
Scud *Gammarus lacustris*	NR	NR	4.5	Sanders, 1969
Scud *Gammarus fasciatus*	NR	0.39	0.30	Sanders, 1970a
Waterflea *Daphnia magna*	0.70	0.60	7.5	Crosby and Tucker, 1966; Sanders, 1970a; Koval'chuk et al., 1971
Seed shrimp *Cypridopsis vidua*	NR	0.18	NR	Sanders, 1970a
Glass shrimp *Palaemonetes kadiakensis*	NR	1.0	15.9	Sanders, 1970a; Chaiyarach et al., 1975
Crayfish *Procambarus clarkii*	NR	NR	14	Cheah et al., 1978; 1980
Crayfish *Orconectes nais*	NR	5.6	NR	Sanders, 1970a
Crayfish *Procambarus simulans*	NR	NR	0.521	Chaiyarach et al., 1975

TABLE 6-1 (cont.)

Species	LC_{50} (mg/ℓ) 24-hour	48-hour	96-hour	Reference
Sowbug *Asellus brevicaudus*	NR	0.40	NR	Sanders, 1970a
Stonefly *Pteronarcys californica*	NR	3.5	0.34	FWPCA, 1968; Sanders and Cope, 1968
Clam *Rangia cuneata*	NR	NR	197	Chaiyarach et al., 1975
Rainbow trout *Salmo gairdneri*	NR	0.29	0.21	FWPCA, 1968; Johnson and Finley, 1980
Carp *Cyprinus carpio*	NR	~9 (72 hour)	NR	Vrochinskii and Zemkov, 1978
Mosquitofish *Gambusia affinis*	0.42	17.0 (72 hour)	16.4	Chaiyarach et al., 1975; Ahmed, 1977; Davey et al., 1976
Channel catfish *Ictalurus punctatus*	NR	NR	33.2	Brown et al., 1979
Green sunfish *Lepomis cyanellus*	NR	34.5 (72 hour)	NR	Davey et al., 1976

TABLE 6-1 (cont.)

Species	LC_{50} (mg/ℓ) 24-hour	48-hour	96-hour	Reference
Bluegill Lepomis macrochirus	NR	0.475	0.32, 19.5	Sanders, 1970a; Johnson and Finley, 1980; Schneider, 1979
Toad (tadpoles) Bufo woodhousii	NR	NR	14.0	Sanders, 1970b
Toad (tadpoles) Bufo bufo	NR	NR	34.0	Nishiuchi and Yoshida, 1974
Unspecified amphibian	NR	15.1	NR	Perevozchenko, 1975

NR = Not reported

muscorum and Anabaena variabilis, during an 18-day exposure period. The only other information regarding effects on aquatic plants was provided by Simonovich et al. (1975). They reported that treatment of soil and water laboratory microcosms with molinate resulted in a decrease in the number of algal species from 66 to 2 over a 40-day period during which the concentrations of molinate in water decreased from 1.83 to 0.028 mg/ℓ.

6.4. RESIDUE

The only information located in the available literature regarding residue was the report by Suzuki et al. (1977), who found concentrations of 0.092 and 0.260 mg/kg, respectively, in the kidney and liver of carp dying in ponds contaminated with molinate after treatment of adjacent rice fields.

6.5. OTHER RELEVANT INFORMATION

Additional relevant information was located concerning bioconcentration, sublethal effects and factors affecting toxicity of molinate in aquatic organisms. Kanazawa (1982) reported that the experimental BCF of molinate in a fish species, the topmouth gudgeon, Pseudorasbora parva, was 26. Numerous Japanese and Russian studies indicate that lethal and sublethal molinate exposure causes anemia in fishes (Popova, 1971; Metelev, 1980; Vrochinskii and Zemkov, 1978; Kawatsu, 1980; Ochiai and Kubota, 1978; Ohtaki and Suzuki, 1977). Investigations concerning factors that affect molinate toxicity indicate that environmental pH has no effect on acute molinate toxicity to carp (Nishiuchi, 1977); however, a patent abstract by the Asahi Chemical Industry Co. (1981) indicates that the addition of an antagonist lowers the toxicity of molinate in field situations. Carp survived >4 weeks in water containing 0.2 mg/ℓ molinate in the presence of menadione sodium bisulfite at 0.2-10 µg/ℓ, whereas 50% of the fish died in <3 weeks when this antagonist was absent.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

According to the Federal Register (FR), a tolerance of 0.1 ppm was established under the Federal Food, Drug and Cosmetic Act for negligible residues of molinate in or on rice and rice straw (32 FR 15107). Two Russian studies reported maximum permissible concentrations in water of 0.02 mg/ℓ, based on odor detection levels (Kosachevskaya and Baran, 1976; Vrochinskii et al., 1975), and one Russian study defined a maximum allowable concentration of 0.75 mg/kg of molinate in soils (Medved et al., 1979).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of molinate were not located in the available literature.

8. RISK ASSESSMENT

No information was available on the carcinogenicity of molinate. Negative results were obtained in some in vitro mutagenicity assays with bacteria both in the presence and absence of a metabolic activating system (Anderson et al., 1972; Shirasu et al., 1976; De Lorenzo et al., 1978). Two abstracts of Russian studies reported that molinate concentrations of 0.02 and 0.2 µg/mL increased the frequency of chromosomal aberrations in human lymphocytes in vitro (Kurinnyi, 1977), and in bone marrow cells of mice at high (unspecified) concentrations (Kuz'menko et al., 1980).

An abstract of a Russian study by Olefir (1978a) reported that repeated exposure of pregnant rats to molinate at 1% of the LD_{50} decreased the activity of the immune system in the first-generation offspring.

The only available information on the effects of chronic and subchronic exposure to molinate are abstracts of Russian studies. Olefir (1973) found significant inhibition of the immunobiological reactivity of rats following oral administration of molinate at 1/20 of the LD_{50}, 5 times/week for 4.5 months. Disorders in the immune system in rats were also reported after 3.5 and 4 months of repeated treatment with molinate at 1/20 of the LD_{50}. Bakhtizina and Latypova (1976) observed morphological and functional changes in rats after chronic treatment with an unspecified dose of molinate. These data are not an adequate basis for the derivation of an ADI value for molinate.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals

with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can, however, be presented in this chapter.

The CBI Appendix to this document reviews a series of chronic toxicity and reproductive studies from which an ADI of 0.0441 mg/day for a 70 kg man (0.63 µg/kg bw/day) was derived. The ADI was based on a NOEL of 0.063 mg/kg bw/day in a 3-generation reproduction study in rats fed molinate in the diet, and an uncertainty factor of 100 (a factor of 10 to account for interspecies extrapolation and 10 for unusually sensitive humans within the population). Higher dose levels (i.e., $\geq$0.63 mg/kg bw/day) produced a detrimental effect on male fertility. The LOAEL for oral exposure to molinate was 0.2 mg/kg bw/day administered to male rats by gavage and was associated with increased resorptions in female rats that were mated to the treated males.

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APPENDIX:

Literature Searched

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
EPCASR
Chemical Industry Notes

Most of these searches were conducted in February, 1983; a few were conducted March-May, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:

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